NEWSLETTER

GeneStroke | The Spanish Stroke Genetics Consortium

Marzo 2014

Nº 10

Estimados compañeros

Os enviamos la Newsletter del consorcio GeneStroke, donde esperamos encontraréis información de vuestro interés sobre las novedades del consorcio y de la genética en el ictus.

Equipo GeneStroke
www.GeneStroke.com

Contenido:

Últimas publicaciones con participación de *GeneStroke:*

Stroke Genetics Network (SiGN) Study: Design and Rationale for a Genome-Wide Association Study of IschemicStroke Subtypes.
Meschia JF, Arnett DK, Ay H, Brown RD Jr, Benavente OR, Cole JW, de Bakker PI, Dichgans M, Doheny KF, Fornage M, Grewal RP, Gwinn K, Jern C, **Conde JJ**, Johnson JA, Jood K, Laurie CC, Lee JM, Lindgren A, Markus HS, McArdle PF, McClure LA, Mitchell BD, Schmidt R, Rexrode KM, Rich SS, Rosand J, Rothwell PM, Rundek T, Sacco RL, Sharma P, Shuldiner AR, Slowik A, Wassertheil-Smoller S, Sudlow C, Thijs VN, Woo D, Worrall BB, Wu O, Kittner SJ; on behalf of the **NINDS SiGN Study.** Stroke 2013 Sep 12.

Exploring the genetic basis of stroke. Spanish stroke genetics consortium.
Giralt-Steinhauer E, Jiménez-Conde J, Soriano Tárraga C, Mola M, Rodríguez-Campello A, Cuadrado-Godia E, Ois A, Fernández-Cádenas I, Carrera C,Montaner J, Díaz Navarro RM, Vives-Bauzá C, Roquer J. Neurología 2013 June 4.

Genes involved in hemorrhagic transformations that follow recombinant t-PA treatment in stroke patients.
Fernandez-Cadenas I, Rio-Espinola AD, Domingues-Montanari S, **Montaner J** et al**.** Pharmacogenomics. 2013 April.

DNA Isolation Method is a Source of Global DNA Methylation Variability Measured with LUMA. Experimental analysis and a systematic review.
Carolina Soriano-Tárraga, Jordi Jiménez-Conde, Eva Giralt-Steinhauer, Ángel Ois, Ana Rodríguez-Campello, Elisa Cuadrado-Godia, Israel Fernández-Cadenas, Joan Montaner, Gavin Lucas, Roberto Elosua and Jaume Roquer. PLOS ONE. 2013 April 9.

PROYECTOS GENESTROKE EN ACTIVO

Actualmente tenemos estos proyectos en curso:

Proyecto: **GLAM-Stroke** (GLobAl Methylation of ischemic stroke)
IP: Carolina Soriano (Hospital del Mar)
Estado: Terminado. En fase de publicación

Proyecto: **GWALA!!** (Bases genéticas de la leucoaraiosis. Estudio de Genome Wide Association en población española)
IP: Jordi Jiménez Conde (Hospital del Mar)
Estado: En fase de análisis volumétricos

¿Quieres realizar un estudio y necesitas colaboraciones? ¡¡¡ Envía tu propuesta !!! ¡PARTICIPAD!

Proyecto: **GWAs GenotPA** (Estudio de Genome-Wide Association en pacientes tratados con tPA)
IP: Israel Fernández Cadenas (Vall d'Hebron Institut de Recerca i Mútua de Terrassa)
Estado: En fase de análisis

Proyecto: **GODS project** (Genetic contribution to functional Outcome and Disability after Stroke)
Coord y IP grupo: Jordi Jiménez Conde (Hospital del Mar); *IP grupo*: Israel Fernández Cadenas (Vall d'Hebron); *IP grupo*: Xavier Estivill (Centro de Regulación Genómica); *IP grupo*: Jerzy Krupinski (Mutua Terrassa); *IP grupo*: Cristòfol Vives (Hospital Son Espases)
Estado: En fase de análisis y replicación

Proyecto: **Cardioembolic Exome** (Secuenciación de exoma completo de pacientes con ictus cardioembólicos)
IP: Israel Fernández Cadenas (Vall d'Hebron Institut de Recerca i Mútua de Terrassa)
Estado: En fase de análisis

Proyecto: **GRECAS Project (**Genotyping Risk and Efficacy of Clopidogrel or Aspirin following Stroke)
IP: Israel Fernández Cadenas (Vall d'Hebron Institut de Recerca i Mútua de Terrassa)
Estado: Replicación completada. En fase de más análisis

Proyecto: **EWAS-Stroke** (Estudio de Epigenome-Wide Association en los subtipos etiológicos de ictus isquémico)
IP: Carolina Soriano (Hospital del Mar)
Estado: Pendiente de genotipado

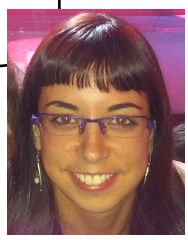
Proyecto: **ChiCHOS** (Case/Control study to analyse tHe genetic risk factOrs of ischemic Stroke)
IP: Israel Fernández Cadenas (Vall d'Hebron Institut de Recerca i Mútua de Terrassa)
Estado: En fase de análisis

Proyecto: **Pharmastroke** (Epigenética en pacientes tratados con antiagregantes)
IP: Israel Fernández Cadenas (Vall d'Hebron Institut de Recerca i Mútua de Terrassa)
Estado: En fase de análisis

Proyecto: **MENEAS** (MEthylation of DNA depending on Nutrition and Exercise habits. Developing a marker of "biological Age" and risk of Stroke)
IP: Jordi Jiménez Conde (Hospital del Mar)
Estado: Financiado. Pendiente de genotipado

Proyecto: **SEDMAN** (Estudio de Seguridad/Eficacia de Dabigatran en fase precoz de ictus, estudio de nuevos MArcadores de Neuroimagen y biomarcadores)
IP: Jurek Krupinski (Mútua de Terrassa)
Estado: Pendiente de financiación

Para solicitar más información sobre los proyectos, podéis contactar conmigo



Marina Mola
(mmola@imim.es)

NOVEDADES SOBRE GENÉTICA EN EL ICTUS:

Multilocus genetic risk score associates with ischemic stroke in case-control and prospective cohort studies.

Malik R, Bevan S, Nalls MA, Holliday EG, Devan WJ, Cheng YC, Ibrahim-Verbaas CA, Verhaaren BF, Bis JC, Joon AY, de Stefano AL, Fornage M, Psaty BM, Ikram MA, Launer LJ, van Duijn CM, Sharma P, Mitchell BD, Rosand J, Meschia JF, Levi C, Rothwell PM, Sudlow C, Markus HS, Seshadri S, Dichgans M. **Wellcome Trust Case Control Consortium 2**. **Stroke**. 2014 Feb.

Abstract

BACKGROUND AND PURPOSE: Genome-wide association studies have revealed multiple common variants associated with known risk factors for ischemic stroke (IS). However, their aggregate effect on risk is uncertain. We aimed to generate a multilocus genetic risk score (GRS) for IS based on genome-wide association studies data from clinical-based samples and to establish its external validity in prospective population-based cohorts.

METHODS: Three thousand five hundred forty-eight clinic-based IS cases and 6399 controls from the Wellcome Trust Case Control Consortium 2 were used for derivation of the GRS. Subjects from the METASTROKE consortium served as a replication sample. The validation sample consisted of 22 751 participants from the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium. We selected variants that had reached genome-wide significance in previous association studies on established risk factors for IS.

RESULTS: A combined GRS for atrial fibrillation, coronary artery disease, hypertension, and systolic blood pressure significantly associated with IS both in the case-control samples and in the prospective population-based studies. Subjects in the top quintile of the combined GRS had >2-fold increased risk of IS compared with subjects in the lowest quintile. Addition of the combined GRS to a simple model based on sex significantly improved the prediction of IS in the combined clinic-based samples but not in the population-based studies, and there was no significant improvement in net reclassification.

CONCLUSION: A multilocus GRS based on common variants for established cardiovascular risk factors was significantly associated with IS both in clinic-based samples and in the general population. However, the improvement in clinical risk prediction was found to be small.

Predicting Stroke Through Genetic Risk Functions: The CHARGE Risk Score Project.

Ibrahim-Verbaas CA, Fornage M, Bis JC, Choi SH, Psaty BM, Meigs JB, Rao M, Nalls M, Fontes JD, O'Donnell CJ, Kathiresan S, Ehret GB, Fox CS, Malik R, Dichgans M, Schmidt H, Lahti J, Heckbert SR, Lumley T, Rice K, Rotter JI, Taylor KD, Folsom AR, Boerwinkle E, Longstreth WT Jr, van Duijn CM, Launer LJ. **Stroke**. 2014 Feb.

Abstract

BACKGROUND AND PURPOSE: Beyond the Framingham Stroke Risk Score, prediction of future stroke may improve with a genetic risk score (GRS) based on single-nucleotide polymorphisms associated with stroke and its risk factors.

METHODS: The study includes 4 population-based cohorts with 2047 first incident strokes from 22 720 initially stroke-free European origin participants aged ≥55 years, who were followed for up to 20 years. GRSs were constructed with 324 single-nucleotide polymorphisms implicated instroke and 9 risk factors. The association of the GRS to first incident stroke was tested using Cox regression; the GRS predictive properties were assessed with area under the curve statistics comparing the GRS with age and sex, Framingham Stroke Risk Score models, and reclassification statistics. These analyses were performed per cohort and in a meta-analysis of pooled data. Replication was sought in a case-control study of ischemic stroke.

RESULTS: In the meta-analysis, adding the GRS to the Framingham Stroke Risk Score, age and sex model resulted in a significant improvement in discrimination (all stroke: Δjoint area under the curve=0.016, P=2.3×10(-6); ischemic stroke: Δjoint area under the curve=0.021, P=3.7×10(-7)), although the overall area under the curve remained low. In all the studies, there was a highly significantly improved net reclassification index (P<10(-4)).

CONCLUSION: The single-nucleotide polymorphisms associated with stroke and its risk factors result only in a small improvement in prediction of future stroke compared with the classical epidemiological risk factors for stroke.

An Adaptive Role for BDNF Val66Met Polymorphism in Motor Recovery in Chronic Stroke.

Qin L, Jing D, Parauda S, Carmel J, Ratan RR, Lee FS, Cho S. **J Neurosci**. 2014 Feb 12.

Abstract

Little is known about the influence of genetic diversity on stroke recovery. One exception is the polymorphism in brain derived neurotrophic factor (BDNF), a critical neurotrophin for brain repair and plasticity. Humans have a high-frequency single nucleotide polymorphism (SNP) in the prodomain of the BDNF gene. Previous studies show that the BDNF Val66Met variant negatively affects motor learning and severity of acute stroke. To investigate the impact of this common BDNF SNP on stroke recovery, we used a mouse model that contains the human BDNF Val66Met variant in both alleles (BDNF(M/M)). Male BDNF(+/+) and BDNF(M/M) littermates received sham or transient middle cerebral artery occlusion. We assessed motor function regularly for 6 months after stroke and then performed anatomical analyses. Despite reported negative association of the SNP with motor learning and acute deficits, we unexpectedly found that BDNF(M/M) mice displayed significantly enhanced motor/kinematic performance in the chronic phase of motor recovery, especially in ipsilesional hindlimb. The enhanced recovery was associated with significant increases in striatum volume, dendritic arbor, and elevated excitatory synaptic markers in the contralesional striatum. Transient inactivation of the contralateral striatum during recovery transiently abolished the enhanced function. This study showed an unexpected benefit of the BDNFVal66Met carriers for functional recovery, involving structural and molecular plasticity in the nonstroked hemisphere. Clinically, this study suggests a role for BDNF genotype in predicting stroke recovery and identifies a novel systems-level mechanism for enhanced motor recovery.

Genome-Wide Genotyping Demonstrates a Polygenic Risk Score Associated With White Matter Hyperintensity Volume in CADASIL.

Opherk C, Gonik M, Duering M, Malik R, Jouvent E, Hervé D, Adib-Samii P, Bevan S, Pianese L, Silvestri S, Dotti MT, De Stefano N, Liem M, Boon EM, Pescini F, Pachai C, Bracoud L, Müller-Myhsok B, Meitinger T, Rost N, Pantoni L, Oberstein SL, Federico A, Ragno M, Markus HS, Tournier-Lasserve E, Rosand J, Chabriat H, Dichgans M.
Stroke. 2014 Feb 27

Abstract

BACKGROUND AND PURPOSE: White matter hyperintensities (WMH) on MRI are a quantitative marker for sporadic cerebral small vessel disease and are highly heritable. To date, large-scale genetic studies have identified only a single locus influencing WMH burden. This might in part relate to biological heterogeneity of sporadic WMH. The current study searched for genetic modifiers of WMH volume in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a monogenic small vessel disease.

METHODS: We performed a genome-wide association study to identify quantitative trait loci for WMH volume by combining data from 517 CADASIL patients collected through 7 centers across Europe. WMH volumes were centrally analyzed and quantified on fluid attenuated inversion recovery images. Genotyping was performed using the Affymetrix 6.0 platform. Individuals were assigned to 2 distinct genetic clusters (cluster 1 and cluster 2) based on their genetic background.

RESULTS: Four hundred sixty-six patients entered the final genome-wide association study analysis. The phenotypic variance of WMH burden in CADASIL explained by all single nucleotide polymorphisms in cluster 1 was 0.85 (SE=0.21), suggesting a substantial genetic contribution. Using cluster 1 as derivation and cluster 2 as a validation sample, a polygenic score was significantly associated with WMH burden (P=0.001) after correction for age, sex, and vascular risk factors. No single nucleotide polymorphism reached genome-wide significance.

CONCLUSIONS: We found a polygenic score to be associated with WMH volume in CADASIL subjects. Our findings suggest that multiple variants with small effects influence WMH burden in CADASIL. The identification of these variants and the biological pathways involved will provide insights into the pathophysiology of white matter disease in CADASIL and possibly small vessel disease in general.

KEYWORDS: CADASIL, cerebral small vessel diseases, genetics, genome-wide association study, leukoaraiosis

CONGRESOS Y REUNIONES DE INTERÉS 2013-2014

American Academy of Neurology Annual Meeting (AAN), April 26, 2014. Philadelphia.

23 European Stroke Conference, May 6-9, 2014. Nice, France.

The European Human Genetics Conference, May 31-June 3, 2014. Milan, Italy.

9th FENS Forum of Neuroscience, July 5-9, 2014. Milan, Italy.

Canadian Stroke Congress, October 4-7, 2014. Vancouver, Canada.

American Society of Human Genetics (ASHG), October 18-22, 2014. San Diego, USA.

9th World Stroke Congress, October 22-25, 2014. Istanbul, Turkey.

Society for Neuroscience (SFN) Annual Meeting: Neuroscience 2014, November 15-19, 2014. Washington DC, USA.

SEN 14- LXVI Reunión Anual de la Sociedad Española de Neurología, Noviembre 2014. Valencia.

XXII World Congress of Neurology, October 31- November 5, 2015. Santiago, Chile.

International Stroke Conference, February 11-13, 2015. Nashville, Tennessee.

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Sugerencias...
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